

Hemodynamics of Hypertension

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THE HEMODYNAMICS OF HYPERTENSION have not been a popular subject for review. In 1938 Wiggers (246) summarized primarily the excellent work of his own group on this subject. It is fitting that a fresh attempt be made to correlate the hemodynamic features of hypertension, particularly as it is evidenced in man, with current physiological concepts. In such a broad coverage, material presented in previous reviews of cardiovascular function must be discussed. It is hoped that these excursions will not be considered a reiteration of the obvious. To provide an organizational framework the hemodynamic features are considered in relation to the various functional subdivisions of the cardiovascular system. Certain aspects not readily covered on this basis are discussed in separate sections.

THE HEART

Cardiac Adaptations to an Elevated Peripheral Resistance

The energy of myocardial contraction is spent in raising the intraventricular pressure sufficiently to maintain a normal stroke output. As the myocardial fibers shorten in systole, their tension diminishes. Eventually a point is reached at which the force generated is less than that of the pressure of blood in the aorta; at this point the aortic valves close and diastole begins (192, 116).

If the peripheral resistance suddenly is increased, for example, by constricting the aorta, the critical systolic pressure level will be reached in an earlier period of ejection. Left ventricular contraction then will end before a normal stroke output has been achieved, and as a result the residual volume of the ventricle will become expanded (174). According to the classical Starling concept, the resulting elongation of the myocardial fibers increases their tension, resulting in an augmented force of contraction (216). After a few beats normal stroke volume is restored and a new equilibrium established characterized by an increased residual volume in both systole and diastole and by an elevated intraventricular systolic pressure. The applicability of Starling's law in the anesthetized open chest dog has been amply confirmed under conditions of increased outflow resistance (244, 198, 99).

The evidence that this simple relationship need not hold except under artificially controlled conditions has been extensively reviewed in recent years (191, 85, 106). Contractile tension at any given fiber length can vary with humoral and neurogenic influences. Shipley and Gregg (208) demonstrated an increase in stroke work independent of filling pressure on stimulating the left stellate ganglion. Sarnoff and his associates have shown that filling pressure-stroke work relations

are characterized by a family of curves (198, 35), the position of any one curve being determined by the experimental conditions. Epinephrine, for example, produced an increase of stroke work at any given filling pressure. On stimulating the left stellate ganglion, a similar change was observed in the relationship between stroke work and estimated diastolic fiber length (157).

Randall and Rohse (181) and Cotton (42) also have shown that stimulation of the left stellate ganglion increases markedly the 'force' of myocardial contraction, producing striking increases in arterial systolic, pulse and diastolic pressures. Despite great elevation of left intraventricular systolic pressure Anzola and Rushmer (6) found a decrease rather than the expected increase in diastolic circumference and a decline in left ventricular diastolic pressure during stimulation of the sympathetic nerves to the heart. Obviously a basic change in the 'contractility' of the myocardium had taken place. The difference between mechanical increase in peripheral resistance and the added factor of a change in myocardial 'contractility' was demonstrated in the following experiment: clamping the aorta resulted in a 90 per cent increase in left ventricular pressure but sympathetic stimulation to the heart during aortic clamping produced an additional increase of 120 per cent with systolic pressures rising to above 300 mm Hg (6).

Left ventricular contractility also can be increased by reducing the perfusion pressure within the carotid sinus (200). Conversely, it is decreased by elevating the carotid sinus pressure or by stimulating the carotid sinus nerves. Sectioning the cardiac sympathetic nerves or administering ganglion blocking agents diminishes these responses. The magnitude of the relative changes in stroke work and peripheral resistance suggests that the cardiac responses to baroreceptor stimulation play an important role in the reflex regulation of arterial pressure.

In the intact, unanesthetized animal the Starling relationship may be quite obscured. During elevation of systolic pressure produced by exercise Rushmer found that diastolic circumference did not always increase; the changes were qualitatively variable even in the same dog during different experimental periods (193). Following epinephrine infusion systolic pressure and stroke volume rose without change in diastolic circumference. In fact, the latter increased when the pressor effects were wearing off. Although intraventricular diastolic volume was not measured, Stead and his associates were not able to establish a direct relationship between right atrial or right ventricular filling pressures and cardiac output in the unanesthetized human subject (217, 218). As estimated by roentgenkymography the end-diastolic transverse diameter of the heart of athletes becomes smaller during exercise (190).

That ventricular contractility is affected in hypertension is suggested by the observations of Wiggers and Katz (245) demonstrating a shortening of the ejection phase with an increase in the velocity of ejection in the intact animal. Increased concentrations of a globulin system have been found in the serum of patients with severe essential hypertension. This increases the treppe phenomenon in the isolated frog heart, producing contracture when sufficient amounts are added (104). The significance of the elevated level of the protein system is obscure and may reflect nothing more than the increased myocardial muscle mass and

cardiac work present in severe hypertension. In the isolated heart preparation Braunwald did not find shortening of ejection with increased outflow resistance (24), but this need not be regarded as proof against its occurrence in the intact animal or man.

Most experimental studies of cardiac adaptation impose short-term elevations of arterial pressure on a heart adjusted to a normal level of peripheral resistance. Essential hypertension in man, however, is characterized by significant left ventricular hypertrophy. It is a reasonable assumption that the tension which the ventricle is capable of developing is proportional to the cross-sectional area of the myocardial wall (33). Such a heart is intrinsically a more powerful pump, that is, it can attain a higher product of pressure times the rate of change of volume, than a normal heart.

The variation in performance between a normal as compared to hypertrophied heart may be quite marked. For example, Beznak (16) found an initial drop in cardiac output following acute experimental coarctation of the aorta in the rat. Cardiac reserve also was compromised in that the maximum elevation of cardiac output obtained with graded infusion of polyvinylpyrrolidone (PVP) solution was reduced immediately following the coarctation. However, in animals with chronic coarctation and resulting myocardial hypertrophy the cardiac output responded normally to PVP infusion. Certain patients with hypertension may sustain high levels of arterial pressure for long periods without significant cardiac dilatation as judged by roentgenography. In such cases autopsy reveals extreme thickening of the left ventricular myocardium (79).

It appears, therefore, that there are at least three possible mechanisms by which the left ventricle might adjust to an elevated peripheral resistance: 1) an increase in residual volume, and, hence, diastolic fiber length; 2) augmentation of intrinsic 'contractility' of the myocardial fibers independent of fiber length, and 3) hypertrophy. Except for the latter, it is not known at present whether one or all of these factors operate in human chronic hypertension prior to the onset of cardiac decompensation. Reliable measurements of left ventricular volume are lacking in living, hypertensive patients. Furthermore, there is no direct evidence that myocardial 'contractility' in human hypertension is abnormally influenced by neurogenic or hormonal factors.

'Cardiogenic' Hypertension

In the final analysis hypertension depends on a disproportion between cardiac output and total peripheral resistance. By substituting a pump with independent controls of stroke volume and rate, it was demonstrated that elevation of stroke volume with corresponding reduction of rate will increase pulse pressure but not mean arterial pressure unless the minute output is elevated (76). While it has been generally assumed that the fault lies entirely in the peripheral resistance, a certain number of hypertensive patients exhibit an elevated minute output and a normal total peripheral resistance (22, 242, 234). It has been mentioned that severe hypertension is observed during stimulation of the sympathetic nerves to the heart. The diastolic elevation is not simply the result of tachycardia, since it occurs when a

constant rate is maintained with an artificial pacemaker (28). Prolonged stimulation of the left cervical ganglion for 5–11 hours leads to a progressive elevation of systolic, diastolic and pulse pressures without significant cardiac acceleration in the anesthetized, open chest dog (185). Rushmer (192) suggests that the elevation of diastolic pressure may be the result of reflexes initiated by the changes in the heart or by liberation into the blood stream of catecholamines released from the myocardium. The latter explanation appears unlikely in view of Celander's observation that the liberation of catecholamines from vascular walls is insufficient to significantly alter the peripheral resistance (36).

The possible role of an augmented 'force' of the heart beat in the genesis and maintenance of hypertension has been suggested in the past (168). Wiggers and Katz (245) observed an increase in the velocity of cardiac ejection in acute experimental hypertension. Of interest in this connection is the reaction of the pulmonary vasculature to increased flow and pressure. Blount *et al.* (20) observed that patients with ventricular septal defects developed pulmonary hypertension with greater regularity than those with atrial septal defects. Pulmonary blood flow was equally increased in both conditions. The difference, therefore, did not lie in the magnitude of blood flow but seemed to be dependent on the intraventricular pressure, which in the case of ventricular septal defect was dominated by the left ventricle. The largest ventricular defects were associated with the greatest elevations of pulmonary arterial pressures. With inter-atrial septal defect flows up to 24 liters per minute do not cause pulmonary hypertension (256). Since the peripheral resistance in the pulmonary circuit is considerably elevated in intraventricular septal defect, whereas in auricular septal defect it is not, these observations suggest some type of interaction between the heart and the peripheral vessels which is not dependent on output alone. The critical factor seems to be the pressures developed in the ventricles and is suggestive of the Bayliss (14), Folkow (68) concept of a myogenic response of arteriolar smooth muscle to pressure. It is not possible, however, to make too literal comparisons between the complicated changes occurring in the pulmonary circulation soon after birth and the development of systemic hypertension.

Cardiac Work and Energy Requirements

It was recognized very early that the work of the heart is increased in hypertension. In 1917 Straub constructed pressure volume diagrams from simultaneous pressure and volume changes in the heart (221). He concluded that the increase in cardiac pump work is nearly proportional to the elevation of systolic pressure and relatively much greater than the increase in mean or diastolic pressure. Similar conclusions were reached by Fahr (60) who calculated work from the potential

energy factor in the equation $w = \int \frac{P_s}{P_{dv}} + \frac{SV^2}{2g}$, and the distensibility curves of

normal arteries. Varnauskas found an increase in left ventricular stroke work in a large series of hypertensive patients subjected to cardiac catheterization (234).

In addition to increased peripheral resistance, per se, there may be other factors which increase the work of the ventricle. Wiggers (246) believes there is a

considerable increase in the velocity of ejection in hypertension (kinetic energy of flow) which is not taken into account in the usual methods for calculating cardiac work. Woods (257) in 1892 and more recently others (30, 85, 199, 33) emphasized the importance of the law of Laplace in relation to the heart. If there is cardiac dilatation the principle radii of curvature of the ventricle will increase. Because of the Laplace equation, $P = T(1/R_1 + 1/R_2)$, greater myocardial tension will be required to produce a given intraventricular pressure. (This interpretation of Laplace's law must be accepted with some reservation, however, as the law applies primarily to situations in which the thickness of the wall is negligible in comparison to the radius of curvature.) Finally, reduction of aortic and large artery distensibility in chronic hypertension causes additional elevation of systolic pressure with a consequent increase in work load.

The considerably added load is reflected in an increased oxygen consumption of the myocardium. Allela *et al.* (4) found that arterial pressure elevation produced much greater increases in cardiac oxygen consumption than did increases in cardiac output. In an elegant series of experiments where either aortic pressure or output was varied with the other held constant, Sarnoff (199) demonstrated that in the isolated 'metabolically supported' heart, oxygen consumption is not related to output but rather to the product of the mean systolic pressure times the duration of systolic ejection, which he calls the tension-time index. In contrast to the results of acute elevations of peripheral resistance in open chest animals, the oxygen consumption per unit weight of heart muscle in patients with chronic hypertension was normal (18, 188). Because of hypertrophy, however, the total weight and hence the total oxygen consumption of the heart probably was increased.

Cardiac Reserve

The older literature indicates that the hypertensive heart is working nearer the limits of its reserve than a normal heart. Wiggers (246) recorded ventricular volume and pressure changes during increases in venous return. In the animal rendered acutely hypertensive, the ventricles were seen to dilate progressively while the systolic discharge at first increased but then decreased. The decompensation began much earlier than in the hearts of normotensive dogs.

While such observations may have their counterpart in acute hypertensive states or in the hypertensive patient with cardiac symptoms, they leave out of consideration adaptive mechanisms, particularly myocardial hypertrophy, which compensate for the elevated arterial pressure in animals (16) or humans with chronic hypertension.

Taylor *et al.* (224) subjected hypertensive patients to relatively strenuous exercise, using a bicycle ergometer. In patients without cardiac symptoms, oxygen uptake, cardiac output, pulmonary arterial and wedge pressures were normal and there was no evidence of decompensation during exercise. The patients with cardiac symptoms tended to have higher oxygen uptakes and lower cardiac outputs at rest, but most exhibited normal pulmonary vascular pressures. However, with exercise all of the latter patients showed evidence of cardiac decompensation as manifested by elevation of pulmonary wedge pressures and a failure of cardiac

output to rise normally. Significantly, the occurrence of cardiac decompensation with exercise bore no relation to the height of the blood pressure, some patients with severely elevated pressures manifesting normal cardiac reserves. Varnauskas (234) also failed to find a correlation between arterial pressure and cardiac reserve in hypertensive patients. It is apparent that aside from such obvious causes as coronary artery sclerosis the factors which determine cardiac reserve in essential hypertension are still not clearly understood.

THE AORTA AND LARGE ARTERIES

The 'Windkessel' Concept

Stephen Hales not only was the first to measure arterial pressure but he also described the function of large arteries as an elastic reservoir converting pulsatile to more continuous flow (105). While not denying that the arterial system is distensible, Peterson's observations (176) indicate that the 'Windkessel' concept has been applied too literally in the past. Large deviations from the differential equation expressing the Windkessel effect were found when the pressure was elevated or depressed beyond the normal range in the living animal. These deviations were thought to be associated with the following factors: the system possesses mass, which must be accelerated when flow rates change; viscous friction is distributed throughout the arterial system, including the distensible vessels, and the gross distensibility of the system varies over wide ranges in living, intact animals. In dogs rendered hypertensive with Neosynephrine and norepinephrine, Peterson found a decrease in aortic distensibility.

Large Artery Distensibility in Hypertension

Wiggers has repeatedly emphasized the importance of the large arteries in the hemodynamic changes associated with hypertension (246, 247). After noting the increased pulse pressure in many hypertensive patients, he points out that 1) in perfusion experiments in models increasing the peripheral resistance actually reduces pulse pressure if the 'central vessels' are composed of distensible materials. Substituting more rigid central vessels raises pulse pressure by elevating the systolic and also lowering the diastolic pressure; 2) pulsatile perfusion of the isolated, normal dog's aorta with increasing pressures up to levels of 200 mm Hg is associated with a decline of pulse pressure, whereas pulse pressure is increased if the aorta is hardened in formalin; 3) the increased pulse pressure in hypertensive patients is not due to an increased stroke volume. Wiggers concludes that clinical hypertension is characterized by a change in large vessel distensibility and is not simply the result of the elevation of peripheral resistance. In acute hypertension produced by vasoconstrictor agents, Wiggers and Wegria found a reduction in the caliber as well as the distensibility of the aorta (247).

Whereas Wiggers' observations in acute hypertension in animals indicated a decrease in aortic and presumably large artery capacity, angiocardiology reveals that in chronic human hypertension the aortic volume characteristically is increased due to both elongation and dilatation (52). This clinical evidence sug-

gests that the loss of distensibility is a secondary rather than a primary effect. Long-continued elevation of pressure within the large arteries results in stretching and a consequent loss of distensibility.

Burton determined the tension changes calculated from the radius and pressure using the law of Laplace ($T = Pr$) in excised rabbit aortas distended with fluid at known pressures (32). These values were plotted against circumference change to obtain an elastic diagram. Such curves were convex to the circumference axis rising steeply in tension as the vessel was distended to its limits. Digesting out the collagen but not the elastic fibers resulted in a curve which did not turn up sharply from the circumference axis. Digesting out only the elastin, on the other hand, increased the initial volume but the tension rose sharply as soon as the wall was stretched. Burton concluded that the elastic fibers control the circumference-tension relationship with small increases in volume, but once the slack has been taken up on the collagen fibers, further increases in volume result in sharp increases in tension. If this is the case, it seems possible that in the dilated hypertensive aorta the tension-circumference relationship might be operating in an area where the less distensible collagen rather than the elastic tissue is playing a predominant role. It is significant that dissecting aneurysm, which is characterized by degeneration of the elastic tissue in the media, is one of the complications of long-standing, severe hypertension. Accelerated atherosclerosis in hypertension is, of course, another obvious cause of diminished distensibility, but it does not explain the increase in pulse pressure seen in young hypertensives. As a result of these changes in large artery distensibility a more pulsatile pressure and flow will be transmitted further into the peripheral vessels.

Coarctation of Aorta

Coarctation of the aorta represents a clinical condition pertinent to this discussion because the vascular beds in the upper and lower halves of the body are subjected to two quite different pressure heads, the upper half bearing the brunt of a considerably higher arterial pressure than the lower half.

In animals the earlier investigators (195, 88, 219) produced a renal type of hypertension with a generalized increase in both systolic and diastolic pressures by constricting the abdominal aorta above one or both renal arteries. Page (167), however, who placed the constricting clamp just below the left subclavian artery in the thoracic aorta (the usual site of coarctation in man) was unable to produce significant hypertension in dogs unless he also clamped the aorta below the renal arteries in order to prevent collateral back flow.

Later investigators (203, 202) were able to produce prolonged coarctations of the thoracic aorta in dogs. Both observed gradual increases in carotid mean pressure reaching a maximum after approximately 2 months, and an early reduction of femoral arterial mean pressure rising to or slightly above the preoperative level at the end of the same period. Removal of one kidney and transplantation of the other to the neck was followed by a reduction of carotid blood pressure to the normal range and of femoral arterial pressure to subnormal levels (202). However, the reduction of blood pressure could be secondary to the debility pro-

duced by such extensive operative interference. In recent experiments on young sheep there was no evidence of a generalized increase in total peripheral resistance after coarctation of the thoracic aorta (203). Systolic, diastolic and mean pressures rose immediately in the carotids while systolic pressure decreased in the femorals. Over the succeeding year, there was no further increase in pressure greater than that seen in the unoperated controls.

The hemodynamic responses following short-term graded constriction of the thoracic aorta just below the left subclavian artery have been investigated by Gupta and Wiggers (98). They noted a marked increase in left ventricular and, to a lesser extent, aortic pulse pressure above the coarctation, and a damping of femoral pressure pulses. They concluded that equally as important as increased resistance are the reduced capacity and distensibility of the aortic compression chamber, and an increase in the systolic discharge of the left ventricle.

Among the earlier clinical investigators of coarctation of the aorta in man, Blumgart (21) and later Bratchmer (23) held that the hypertension is due to the increased resistance afforded by the coarctation and long collateral circulation. However, Steele (220) using direct intraarterial recording of pressure found diastolic pressures ranging between 110 and 132 mm Hg in the brachial and 90 to 120 mm Hg in the femoral arteries in three patients. He interpreted these levels of diastolic pressure to indicate a generalized increase in peripheral vascular resistance.

In light of later investigations on larger series of patients (17, 27, 108, 45) it appears that Steele's cases exhibited pressure levels which were significantly higher than the rule. The pooled data on the 57 cases studied by these investigators reveal average diastolic levels in the brachial arteries of 90 to 100 mm Hg and in the femorals in the range of 70 to 90 mm Hg. There were a few patients in each series with femoral diastolic levels in the hypertensive range. The elevations were slight, however, and might be explained on the basis of damping. Slight elevations of diastolic pressure can be produced by a partial occluding cuff placed proximally on an extremity (250, 118). Although the diastolic pressure often is slightly elevated in the upper extremities, the predominant feature is an increase in pulse pressure with proportionately greater elevations of systolic rather than diastolic pressure (17, 27, 45) similar to the findings of Gupta and Wiggers in animals (98).

Whereas Bing and his associates (17) found the blood flow elevated in the forearm and reduced in the calf, Lewis (145) and Wakim *et al.* (236) observed normal levels of blood flow in both the upper and lower extremities. Pickering (177) also found normal blood flow in the upper extremity. More recently Patterson *et al.* (173) found normal levels of blood flow in the forearm and calf. Also, in contrast to the abnormalities of capillaries frequently seen in essential hypertension, the nailfold and toe capillaries appeared normal in patients with coarctation (152). The consensus, therefore, seems to indicate that blood flows in the extremities do not deviate significantly from the normal range, which in the presence of the mean pressure differences in the upper and lower limbs indicates that peripheral resistance is higher above than below the coarctation.

In regard to renal hemodynamics in coarctation, two groups of investigators reported the pattern seen in essential hypertension, namely, reduced renal blood flow and normal glomerular filtration rate (80, 86). However, the latter group (86) did not believe that the hypertension was due to renal ischemia, and, in fact, additional data on these same patients (17) indicated that the peripheral resistance (exclusive of the coarctation and collateral circulation) was not only below normal but also was unequal, being higher above than below the coarctation. In addition, others have found that the renal plasma flow and glomerular filtration rate usually were normal (108, 231, 126). In the few instances in which renal plasma flow was reduced the filtration rate also was correspondingly reduced unlike the pattern seen in essential hypertension.

Culbertson *et al.* (45) estimated hepatic portal blood flow almost simultaneously with the measurement of cardiac output. In 10 patients 6 showed elevations of both the cardiac index and hepatic portal blood flows; two had normal values and two showed reductions of both parameters. The calculated splanchnic vascular resistance was subnormal in all cases, which was in sharp contrast to the increased resistance observed previously by Culbertson and his associates in patients with essential hypertension (46, 252).

Several investigators report the cardiac output to be normal or increased (97, 17, 15). Culbertson (45) found elevated cardiac outputs in the majority of his patients, and in the two in which it was reduced there were other evidences of early cardiac failure. The elevated pulse pressure above the coarctation is consistent with the presence of a high stroke volume. It seems likely that the dilatation and loss of distensibility of the aorta above the coarctation and the increase in stroke volume both play a part in producing the characteristic increase in pulse pressure in the upper extremities.

It is not definitely known whether the nice adjustment of resistance is mediated through neurogenic or local influences. Unfortunately, the effect of blocking the vasomotor nerves either locally or generally, such as with ganglion blocking agents, has not been studied. However, the distribution of the adjustment with vascular resistance sharply differentiated between the upper and lower halves of the body does not fit the pattern of any known form of vasomotor response. The regulation is most likely due to local factors, with each vascular bed altering its basic resistance autonomously so as to assure a sufficient but not excessive blood flow for local tissue needs. A myogenic response of arterioles to pressure could account for this self-regulation, but so could tissue oxygen tension or the local production of vasodilator metabolites.

PERIPHERAL RESISTANCE

Biophysical Considerations

The discrepancies in the Poiseuille equation relating resistance to pressure and flow have been discussed by numerous investigators (93, 171, 248, 31). When a vascular bed is perfused at increasing pressures and the pressure is plotted against flow, the relation is not a straight line passing through the origin as would be expected if the Poiseuille relation strictly applied. There are two principal departures

from linearity: 1) no flow occurs until the pressure is raised to approximately 10–20 mm Hg, and 2) the increment of flow becomes progressively greater with increasing pressures so that the curve is convex to the pressure axis, indicating a progressive reduction in resistance as the perfusion rate is increased. This is demonstrable not only in isolated vascular beds, but also during perfusion of the entire systemic circulation (76). In glass tubes with diameters as small as 0.05 millimeter flow begins as soon as there is a perceptible pressure difference (93). The absence of flow at pressures below 10 mm Hg in living tissues had been explained on the basis of plastic flow in capillaries. Since the capillaries have diameters approximately the same as red cells a significant pressure difference was considered necessary to overcome the elastic resistance of their walls to the passage of the red cells (138). However, Burton (31) has substituted the concept of critical closing pressure in small vessels to explain this departure from Poiseuille's law. He defines the forces which govern the diameter of a blood vessel as a balance between the distending force of the effective blood pressure and the closing force of the tension in the vessel wall. According to the law of Laplace, tension is proportional to the pressure times the radius of the cylinder of blood vessel. As the radius becomes small, less tension is required in the wall to resist the internal pressure. When pressures fall to low values the tension in vessels of small radius, such as arterioles, is sufficient to result in complete closure. Since it is theoretically impossible for a hollow tube with walls of finite thickness to close entirely Burton postulates that the endothelial cells round up and fold on each other to effectively obliterate the lumen.

The second departure from Poiseuille's law, namely that of disproportionately large increases in flows with increasing pressures, has been explained variously on the basis of apparent viscosity changes and on the elastic properties of vascular walls. When blood is made to flow through glass tubes of a diameter smaller than 0.3 millimeter the apparent viscosity relative to water progressively decreases with decreasing diameter of the tube (61). Similarly, in such small tubes the apparent viscosity changes as flow increases from low values up to some rate, and thereafter remains constant (93). This is probably due to the fact that at increasing velocities the cells are thrown into the center of the stream, leaving the lower viscosity plasma near the wall. From recent studies Haynes (109) has concluded that at the pressures and flows normally existing in the cardiovascular system changes in apparent viscosity would have a negligible influence on peripheral resistance.

Levy perfused the dog's hind limb with blood and homogeneous perfusates over a wide range of pressures while maintaining a constant AV pressure gradient (144). Essentially similar results were seen using either blood or homogeneous perfusates, in that parallel increases in arterial and venous pressure resulted in parallel falls in resistance. These observations also argue against the importance of 'plastic flow' or changes in apparent viscosity due to the presence of red cells as playing a significant part in the observed departures from Poiseuille's law.

Burton (31) finds that the shape of pressure flow curves obtained in living vascular beds is due to the structural characteristics of arteriolar walls. Smooth muscle is viscoelastic. When it is stretched suddenly, considerable tension develops

immediately, but if the length is kept constant this tension disappears. Smooth muscle has such a low modulus of elasticity that it could not resist the internal blood pressure. Resistance to stretch, or 'elastic tension,' is provided by elastic tissue for small pressure variations, and by the collagen tissue 'jacket' at higher pressure variations. The function of the smooth muscle is to provide 'active tension' through contraction or relaxation, which adjusts the jacket of elastic and collagenous tissue. In this way Burton explains the markedly different pressure flow curves obtained in the same vascular bed when it is in a vasoconstricted or vasodilated state (31, 93). The much steeper rise in pressure per increment of flow in the vasoconstricted vascular bed is considered to result from first, an increase in wall tension as a function of decrease in radius (Laplace equation) and secondly, the fact that the smooth muscle pulls in the pressure-resistant fibers of connective tissue. Hypertrophy and fibrosis of arteriolar walls in chronic hypertension also would diminish distensibility.

Burton implicates the arterioles as the sole controlling influence in the alteration of pressure flow curves caused by sympathetic stimulation or vasoconstrictor drugs (31). This view does not take into account the significant changes in vascular capacity which occur with such stimulation (see discussion in later section). Closure of precapillary sphincters as well as venular and venous constriction reduce the volume of the entire vasculature being perfused. This decrease in capacity could contribute to the observed shifts in the pressure flow curves with vasoconstrictor stimuli.

Anatomical Distribution of Peripheral Resistance

As indicated by the continuous pressure drop from the aorta to the venae cavae the vascular resistance is not limited to the arterioles but is distributed in varying degree throughout the systemic circulation. Approximately twenty per cent of the peripheral resistance lies in the larger vessels proximal to the arterioles (248). However, the minute vessels, including arterioles, metarterioles and capillaries constitute the chief areas of changing peripheral resistance. Direct observation of the small vessels in a variety of living animals, and in different vascular areas (146, 162, 3, 258) reveal certain common characteristics: 1) Vessels of like kind anastomose with each other, forming arterial arcades, capillary networks, and venular and venous interconnecting channels, thereby producing varying patterns of flow from moment to moment depending on slight pressure fluctuations. 2) Where the capillary network takes origin from the metarterioles a cuff of smooth muscle is attached which acts as a sphincter alternately opening and closing asynchronously with neighboring capillaries to produce intermittency of flow in individual capillaries. 3) Direct arteriovenous communications are found in greatest numbers in specialized tissues such as the skin of the distal parts of the extremities, but 'thoroughfare passages' between metarterioles and venules are seen in almost all tissues. 4) The arterioles and metarterioles are capable of wide variations in caliber and under adequate local stimulation are capable of closing off completely or dilating widely. Under resting conditions their caliber is seen to vary slightly from time to time, usually asynchronously with neighboring arterioles.

It is apparent that measurement of the total resistance change from the over-all flow to a tissue and the large artery to large vein pressure difference supplies no information regarding the activities of the various subdivisions of the small circulation. Even such relatively crude measurements as the small versus large artery and small versus large vein pressure differences have disclosed qualitatively different and sometimes opposing changes in peripheral resistance of large versus small vessels in response to pH changes (64) and to serotonin (103). The apparent constancy of the peripheral resistance under basal conditions is the result of intermittently fluctuating resistances occurring out of phase in a multitude of small vessels.

Calculated Peripheral Resistance in Hypertension

The evidence indicates that in most hypertensive patients the peripheral vascular resistance is increased and that this increase is fairly uniformly distributed throughout the body. When the cardiac output and mean arterial pressure are determined in uncomplicated hypertension using modern methods the cardiac output usually is normal and the total peripheral resistance is elevated (90). However, the total peripheral resistance is by no means invariably elevated and a relatively high cardiac index has been observed in some hypertensive subjects (22, 242, 234). In a large series of hypertensive patients Varnauskas (234) found that 36 per cent had peripheral resistance values within normal limits. Such observations suggest the possibility that in its early stages hypertension may be associated with an increase in the minute output of the heart. However, no correlation was found with the severity or duration of the hypertensive disease; and apprehension associated with the procedure may have transiently elevated the cardiac output above the resting level.

In chronic human hypertension, with the exception of the kidney, where plasma flow usually is slightly to moderately reduced (213, 234), cerebral blood flow (123, 207, 107), coronary circulation (18, 188), extremity (177, 179) and hepatic portal circulation (46, 252) are all within the normal range. There is, therefore, no evidence from these major vascular areas to support the observation that the total circulatory rate may be increased in some patients with hypertension. The elevated peripheral resistance seems to be uniformly distributed except in the kidney, where it appears to be slightly more intense.

Direct Observation of Small Vessels

Abnormalities of the small vessels have been described in hypertensive patients by a number of investigators. In the conjunctivae these abnormalities include diminished number of visible capillaries (189), abnormally thin and tortuous capillaries (132, 140, 137), constricted terminal arterioles and metarterioles which exhibit increased reactivity to topical epinephrine (140, 119), and increased intermittency of capillaries (119). Any one of these changes is seen occasionally in normal individuals, but the presence of all features is characteristic of hypertension (140), and they were seen with much greater frequency in hypertensive patients (137). Thinning of capillaries was not directly associated with the severity of the

hypertension. Very thin capillaries also have been seen in the nailfolds of hypertensives (137) and the critical closing pressure of digital small vessels is elevated (84) as compared to normotensive individuals. Diminished vascularity of the small intestine has been seen in postmortem injection studies in a small series of hypertensive patients (209).

It must be emphasized that the small vessels of the bulbar conjunctiva, and especially the nailfold, may not be representative of the total peripheral vasculature. However, these observations provide at least some information as to the sites of increased resistance in the small vessel circulation. It is of considerable interest that the capillaries, which are commonly regarded as 'capacity' rather than 'resistance' vessels, seem to be involved as well as the arterioles.

Factors Controlling Peripheral Resistance

Local factors. As the transportation system of the body the circulation is remarkably efficient in adjusting traffic in any area to the needs of the moment. It has been shown that the distribution of the cardiac output and the level of blood flow in various body regions remains essentially normal in hypertension and that the peripheral resistance is generally elevated so as to provide this normal distribution. In coarctation of the aorta a remarkable adjustment is made so that the upper and lower portions of the body have quite different peripheral resistances in order to assure an equitable distribution of blood flow. Numerous examples in the literature attest to the facility with which the peripheral resistance can be adjusted to changing pressures in order to preserve a normal blood flow. Vessels of the hind limb or intestine of the cat dilate after only 3-5 seconds of proximal occlusion (113). Direct observation of the pial arterioles through cranial windows in the cat revealed vasoconstriction on elevation and vasodilation on reduction of blood pressure to the head (65, 66, 70, 7).

In man (95, 37, 184, 206) small degrees of venous congestion of the extremities reduce rather than increase resistance. However, larger degrees of congestion as produced by a cuff (172) or exposing the limb to subatmospheric pressure (94) are associated with an increase in resistance whether measured during (34) or after (38) the procedure.

At least some of these responses do not depend upon neurogenic influences. The vasodilation which follows brief occlusion in the hind limb of the eviscerated cat is not dependent on sympathetic supply or axone reflexes (67, 68). Sudden sustained increases or decreases of flow and pressure in arteries supplying skeletal muscle in the dog resulted at first in a large transient increase or decrease, respectively, of blood flow due to passive changes, followed within 1-2 minutes by a return to a steady level near the original flow rate (215). Acute denervation did not affect these responses. That postarteriolar vessels also may share in this response is suggested by an experiment in which increased flow was diverted to a vein in the bat's wing. Increased frequency of cyclical venoconstriction followed this increase in flow and pressure (241). Vasomotion in the bat's wing has been shown to be independent of nerve supply (161, 240). Return to normal flow and resistance have been observed in the hand (10) and in the forearm and calf circu-

lations of man following sympathetic denervation (11, 91, 249). However, in the toes, whose circulation seems to be dominated completely by vasoconstrictor nerves, sympathectomy usually results in a lasting vasodilation (87, 147). As Folkow (69) has pointed out, the return of vascular tone in the muscles can hardly be explained on the basis of increased reactivity to circulating catecholamines following denervation since the digital vessels are unusually responsive to such substances and would be expected to react more profoundly than muscle vessels.

It is beyond the scope of this review to present in detail the evidence regarding autonomy of tone in the absence of neurogenic influences in such areas as the kidney (212) or the brain (125), or to do more than indicate that the regulation of normal flow rates, and, hence, vascular resistances can be independent of the autonomic nervous system. Whether this autonomy is due to a 'myogenic response' or to local metabolic alterations is a matter of fundamental importance in understanding the factors that control peripheral resistance. Presently available evidence indicates that the controlling metabolic factors may vary from one vascular bed to another. For example, in the brain carbon dioxide appears to be a dominant factor (124, 201), but in the coronary circulation it is less important than oxygen tension (96). Opinion is sharply divided concerning the validity of the myogenic response since it is difficult to separate experimentally the effects of alterations in pressure, per se, from metabolic changes.

Neurogenic control. In Folkow's excellent review of nervous control of the blood vessels (69) evidence is presented that vasomotor regulation is carried out predominantly by sympathetic vasoconstrictor nerves which make up the effector arm of the baroreceptor reflexes. There is no good evidence for centrally mediated impulses acting through dorsal root vasodilator fibers, the latter being involved in axone reflexes only. Sympathetic vasodilator fibers supply voluntary muscles exclusively and are not concerned with homeostatic, baroreceptor responses. Under normal circumstances the contribution of the adrenal medulla or of catecholamines released from vascular walls is judged to have insignificant effects on peripheral resistance.

Von Euler found the norepinephrine output in the urine (235) to be normal in 84 per cent of 500 patients with essential hypertension. The elevations found in the remaining 16 per cent were not thought to be sufficient to produce significant hypertension. If generalized sympathetic vasoconstriction were present in hypertensive patients, then sympathetic denervation of a vascular region should be followed by an abnormally increased blood flow to that part. However, unilateral splanchnic and lumbar sympathectomy does not elevate the resting blood flow to the sympathectomized calf to a level greater than normal (249). Intravenous tetraethylammonium fails to produce a greater decrement in the peripheral vascular resistance of the forearm and foot in hypertensive as compared to normotensive subjects (129). Increased blood flow does not occur in the hypertensive kidney after sympathectomy (1, 40). Estimated hepatic portal blood flow increases immediately after lumbodorsal splanchnicectomy in hypertensive patients, but then returns to preoperative levels after several months (252). Bilateral nerve block of the cervical sympathetic chain fails to alter the elevated cerebrovascular resistance in hypertension (107). These observations in various vascular areas lend no sup-

port to the concept that catecholamine production or vasoconstrictor nerve hyperactivity has any etiologic importance in the elevation of peripheral vascular resistance seen in chronic essential hypertension. The transient increase in hepatic portal blood flow might be expected to occur as well in normotensive individuals since such splanchnic vasodilation occurs in normotensive animals after sectioning the splanchnic nerves.

Moderator reflexes. Although the evidence points away from increased vasoconstrictor nerve activity as a cause of the increased vascular resistance, nevertheless it is probable that the homeostatic regulating mechanisms are reset to maintain a higher level of blood pressure in essential hypertension. A resetting of the level at which the baroreceptor reflexes will respond does not imply sympathetic hyperreactivity. Indeed, in such a situation the rate of efferent vasoconstrictor discharges would be increased only by sudden reductions of blood pressure toward normal levels. Sudden alterations in cardiac output such as may be induced by the Valsalva maneuver or by postural changes (251, 72) or by venous congestion of the extremities (73) results in prompt vasoconstrictor or vasodilator responses, as the case may be, to maintain the blood pressure at the preexisting hypertensive level. These rapid homeostatic vasomotor adjustments are similar in hypertensive and normal individuals except that the level to which the arterial pressure is adjusted differs in the two groups. That these quick responses are under the control of the sympathetic nervous system is indicated by the fact that they can be abolished by lumbar splanchnicectomy (251) or by drugs which inhibit sympathetic nerve transmission (63, 73). In dogs when the splanchnic nerves are stimulated continuously for many hours the heart rate, which slows at first, gradually returns to normal (131). Following cessation of stimulation the heart rate becomes rapid as the blood pressure returns toward normal levels. This suggests that after several hours the baroreceptors recognize the elevated level of blood pressure as being normal.

More direct experimental evidence for a resetting of the carotid sinus baroreceptors has been provided by McCubbin, Green and Page (150). The effects of various levels of perfusion pressure applied to the isolated carotid sinus were compared in normotensive and renal hypertensive dogs. Reflex depressor responses were obtained in the hypertensive animals only at higher perfusion pressures than were required in the normotensive dogs. Action potentials recorded from the afferent nerve fibers indicated that the baroreceptor nerves were stimulated at significantly higher perfusing pressures in the chronically hypertensive than in the normotensive animals. These observations are consistent with the altered 'set' of the reflex vasomotor responses in hypertensive patients. They may also explain the persistence of hypertension which may occur after a known primary cause, such as a pheochromocytoma or unilaterally diseased kidney, has been removed (178); or why long continued antihypertensive drug therapy often seems to moderate the basal level of blood pressure (175). The possibility also is raised that the primary etiologic factor or factors in hypertension could be episodic, with blood pressure sustained at high levels between episodes through a resetting of the baroreceptor mechanisms (170).

Heymans has proposed that hypertension may be initiated by a change in the

distensibility of the carotid sinus (111). This proposal is based primarily on his observations that changes in the tension of the carotid sinus produced by injecting various constrictor or dilator agents into the wall of the sinus result in blood pressure alterations opposite in direction to the effect of these agents given systemically. Recent evidence (143) indicates, in contrast to previous work, that the hypertension which follows section of the moderator nerves is not due to an increase in cardiac output, but rather to an increased peripheral resistance.

Heymans' concept implicates the carotid sinus as the prime mover in the hypertensive process. This hypothesis necessarily implies that the hypertension is initiated and maintained by increased rates of sympathetic vasoconstrictor nerve discharge. It should be noted that the evidence previously discussed suggests that elevated vascular resistance in human chronic hypertension does not seem to be associated with increased activity of the sympathetic nervous system. However, sympathetic hyperactivity is not essential to the concept that some mechanism other than the carotid sinus initiates the increase in peripheral resistance and that the resulting hypertension is subsequently aided and abetted, or even maintained, by a resetting of the level at which the carotid sinus and aortic arch reflexes will respond.

Cation and water content of vascular walls. Recently Tobian (229) has proposed that the increase in peripheral resistance is due to the accumulation of sodium in arteriolar walls, which in turn attracts water and leads to a 'waterlogging' of the arteriolar walls, thereby narrowing their lumina. Tobian and Binion found increased sodium and water concentrations in the renal artery and psoas muscle of hypertensive patients (226) and in the aortas of hypertensive rats (230). In the latter the concentrations of potassium, magnesium and phosphorus also were increased per unit of cell protein (227). Tobian also found an increase in the sodium concentration of the femoral arteries of dogs made temporarily hypertensive with infusions of norepinephrine (228).

Other investigators, however, have reported different findings. As compared to normal controls Daniel and Dawkins (50) found no disturbances in aortic wall concentrations of electrolytes in spontaneous, renal constriction and long standing DCA hypertension in rats. Only in the early phase of DCA hypertension a reduction in potassium concentrations occurred in the smooth muscle of the aortic and gastric walls, with an inconstant trend toward increased sodium concentration. The water and sodium content of cardiac and skeletal muscle increased in the animals with constricted kidneys whether they became hypertensive or not. Freed and his associates (71) also failed to observe a significant elevation of sodium in the aortas of renal hypertensive rats, although they do report an increased potassium content.

Under conditions of constant blood flow in the forelimb of the dog Haddy *et al.* (102) demonstrated a decrease in arteriolar resistance with increasing concentrations of sodium in the perfusing blood. Arteriolar resistance varied inversely with sodium concentration both above and below the normal range of sodium concentration in blood. The intravenous infusion of hypertonic saline solutions results in systemic hypotension (58). The mechanism of the antihypertensive effects of diets very low in sodium (159, 163, 239) and of natriuretic agents such

as chlorothiazide in hypertensive man (77, 223) seems to depend primarily on reductions of plasma volume and total extracellular fluid. The decrease in arterial pressure after chlorothiazide is associated with a fall in cardiac output (44, 56). Right atrial pressure is reduced (44), which in the presence of a lowered cardiac output implies a decrease in venous return. Such effects can be explained on the basis of reduced plasma volume. A decrease in extravascular tissue pressure consequent to loss of extracellular fluid volume may be an additional factor. Restoration of the plasma volume with salt-free dextran solutions promptly reverses the antihypertensive effect of chlorothiazide (78) and does away with any postural hypotension associated with the rice diet (164). Elevating the legs (44) or infusion of salt-free dextran (56) restores the cardiac output. After chlorothiazide in hypertensive patients the excess sodium which is excreted appears to be derived primarily if not entirely from the extracellular rather than intracellular fluids (78). These various observations in hypertensive man do not indicate that salt-depleting procedures affect blood pressure by reducing arteriolar resistance or by lowering intracellular sodium content.

Friedman and his associates (81, 82) have detected a reduction in extracellular sodium and an increase in potassium when blood pressure is elevated with norepinephrine, vasopressin or angiotensin in animals. Reducing the sodium concentration in the fluid bathing strips of rat colon (83) and of guinea pig uterus (117) produces an immediate increase in smooth muscle tension. This is followed by a relaxation to the basal tension as sodium ion equilibrates inside and outside the cells (83). Conversely, drug-induced smooth muscle contraction is abolished immediately after the sodium concentration of the medium is increased. Arterial pressure is reduced transiently during rapid intravenous infusion of hypertonic sodium solutions in rats (83). Friedman concludes that the tension developing in smooth muscle of vascular walls varies directly with the ratio of sodium concentration inside the cells to that outside. According to this concept hypertension is characterized by abnormal intracellular accumulation of sodium ion in vascular smooth muscle, leading to increased vasoconstrictor tone. This hypothesis differs from Tobian's concept that an excess of sodium produces narrowing of the lumen by hydrating the vascular wall.

It should be noted, however, that tension also is increased in strips of rabbit carotid artery by reducing the potassium content of the surrounding fluid (141). The nature of sodium and potassium shifts during smooth muscle contraction are extremely complex and their importance in the regulation of vascular tone is still obscure. Finally, it should be pointed out that the concentrations of cations in the extracellular fluid are normal in uncomplicated essential hypertension and that evidence is lacking for a change in intracellular concentrations.

CAPACITY VESSELS: CAPILLARIES, VENULES AND VEINS

According to the older literature the venous system contains 75 per cent of the blood volume, of which the largest proportion is in medium and large sized veins (93). More recent data, however, indicate that the largest proportion of the blood volume is in the small vessels, including venules and small veins (127, 156).

Helically cut strips of peripheral veins of dogs exhibit strong contraction

with vasopressor agents (142). In the perfused hindlimb of the dog norepinephrine infusion produces an initial gain in hindlimb weight and arterial pressure, indicating arteriolar constriction followed quickly by a marked loss of weight brought about by constriction of the postarteriolar vessels (205). A similar decrease in weight following norepinephrine has been observed in the liver and in an intestinal loop (148). Haddy (101) measured the wedge pressures in small (0.5-mm diameter) arteries and veins as well as the lateral pressure in large arteries and veins in the foreleg of the dog. Blood flow was maintained constant with a pump interposed in the brachial artery. In 'physiologic' doses, by constant infusion, norepinephrine (but not epinephrine) elevated small vein as well as arterial pressures. The calculated resistance increased in each segment, including the small vein segment.

Sympathetic nerve stimulation also decreases the capacity of postarteriolar vessels. A rise in pressure and a decrease in the diameter of venules and small veins have been observed by Visscher and his associates (139, 122). Venous constriction also may be obtained reflexly; occlusion of one or both carotid arteries in dogs under chloralose anesthesia increases the pressure in a miniature balloon inserted into a peripheral vein (196).

A number of investigators using a variety of techniques have demonstrated a shift of blood volume into the central circulation following infusion of catecholamines (197, 186, 182, 100). This shift is presumably due to constriction of the capacity vessels. Ganglion blocking agents, on the other hand, increase the capacity of the peripheral vessels (197, 186, 232). Similar shifts of blood volume from the peripheral to the central circulation have been produced by carotid artery occlusion in adrenalectomized dogs with denervated lungs (49). The reverse occurs when the carotid sinus is perfused under increased pressure (48). Alexander has indicated that venomotor tone is increased after hemorrhage (2).

In man, several investigators have observed that isolated venous segments in the intact forearm constrict after reflex stimulation (55, 166). Wood and Eckstein demonstrated venoconstriction in the forearm in response to pooling of blood in the legs (254). Epinephrine, norepinephrine, ephedrine and angiotensin (but not vasopressin) elevated pulmonary artery and pulmonary wedge pressures in man, suggesting a central shift of blood volume produced by these pressor agents (160). When the sympathetic vasoconstrictor nerves are inhibited in man by administration of hexamethonium, the arterial pressure falls not only because of arteriolar relaxation but also because of reduction in right heart pressures and cardiac output (75, 243). In such individuals the arterial pressure becomes a direct function of the blood volume, and withdrawals of as little as 2-4 per cent of the total blood volume results in perceptible decrements of arterial pressure (73).

These reactions are concerned with the homeostatic adjustments of the organism to postural changes and as an emergency protective device to sustain central blood volume in the event of violent exercise or of hemorrhage. Certain types of heart disease associated with a reduced cardiac output also may activate a peripheral venoconstrictor response (74, 29, 255, 121). The afferent arm is, at least in part, the baroreceptor on the arterial side of the circulation. Systemic venous

constriction apparently is not involved in light and moderate exercise to any appreciable extent, the residual volume of the heart and the pulmonary blood volume providing a sufficient reservoir (211, 8).

The so-called 'intrinsic' blood pressure has been measured in the brachial artery and antecubital vein of hypertensive patients after occlusion of the circulation produced by rapid inflation of an arm cuff. The time required to obtain an equilibrium between arterial and venous pressure was approximately 30 seconds. Anderson (5) found the intrinsic pressure to be elevated in slightly more than half of patients with chronic hypertension uncomplicated by cardiac failure. Lanari *et al.* (135) also found the intrinsic pressure significantly elevated in asymptomatic hypertensive subjects as well as after norepinephrine infusion or reflexly induced vasoconstriction in normal subjects. On the other hand, infusion of blood into the brachial artery of the occluded arm produced sigmoid pressure-volume curves which were essentially the same in hypertensive and normotensive subjects (136). However, because of the long period of occlusion considerable changes in tone could occur during the latter measurement.

While there are ample data to indicate a decrease in the size of the capacity vessels as a result of sympathetic stimulation or infusion of catecholamines, the evidence in chronic hypertension is only sketchy and suggestive. Such evidence includes the direct observations of capillary thinning and diminished vascularity in the nailfold and the conjunctival vessels, the elevation of intrinsic blood pressure, the increased responsiveness of hypertensive patients to reductions in plasma and extracellular fluid volume, and the presence of exaggerated natriuresis following small infusions, which is discussed in a later section. A decrease in peripheral vascular capacity may occur in acute hypertensive states, such as acute glomerulonephritis or preeclamptic toxemia of pregnancy, where the central venous pressure is often found to be elevated. A significant contraction of peripheral capacity vessels should divert enough blood into the central circulation to elevate central venous pressures. However, in chronic hypertension prior to cardiac decompensation central venous and pulmonary arterial pressures are normal.

It is possible in chronic hypertension that the left ventricle could elevate cardiac output for a brief period long enough to transfer the increased central blood volume to the arterial side of the circulation. Following this transfer a new equilibrium would be established, in which central volume and cardiac output return to normal whereas arterial pressure and volume are further elevated. An increase in aortic diameter has been observed in hypertension (52) but the extent of this dilation does not seem sufficient to accommodate a significant transfer of blood volume without participation of other large arteries.

VASCULAR REACTIVITY

Following the demonstration of Hines (112) that the 'cold pressor' response is increased in hypertensive patients, there has been considerable interest in the problem of vascular reactivity in hypertension. The cold pressor test involves a complex response which includes not only reflex vasoconstriction but also pain perception and possibly an adrenergic discharge. Using stimuli involving only

homeostatic vasoconstrictor reflexes Wilkins and Culbertson (251) found great variability in the hypertensive 'overshoots' from one patient to another. There was no definite separation between hypertensive and normotensive subjects in the percentage elevation of blood pressure. Hypertensive patients exhibited slightly greater pressor responses to angiotensin and *s*-methyl-iso-thiourea (53), but the difference was maintained after ganglionic blockade with hexamethonium. A wide range of responsiveness was observed in both groups. An increased pressor response to norepinephrine in hypertensive patients was observed by Goldenberg *et al.* (89) but this was not confirmed by Judson, Epstein and Wilkins (120). According to Conway (39) pressor responses to norepinephrine were similar in normal and hypertensive rabbits so long as the moderator reflexes were operative. After methonium blocking the hypertensive animal showed the greater increase. Increased peripheral vasoconstriction following infusion of catecholamines has been reported in local vascular beds such as in the quadriceps muscle (158), the hand (54), and by Mendlowitz (153) in the maximally vasodilated digits of hypertensive patients.

Vascular reactivity has been studied to some extent in animals. Page *et al.* (169) found that hepatectomy usually reduced rather than enhanced vascular responsiveness to pressor agents, despite the fact that the liver is an important detoxifying organ. Obvious factors such as hemorrhage did not seem to account for these results. The reactivity to norepinephrine is variably but significantly increased in the hind limb of dogs with renal hypertension and in hypertensive rats (151, 165). In renoprival hypertension in dogs increased reactivity to pressor drugs may have been related to an elevated serum potassium concentration (130). Reduction of serum potassium levels in normal dogs using glucose and insulin lowered their pressor reactivity.

The sodium content of the body also seems to play some role in vascular reactivity. Raab and associates (180) observed that sodium restriction reduced the pressor response to norepinephrine infusion in hypertensive patients. This has been disputed by Dahl (47). Increased reactivity to norepinephrine has been seen in adrenalectomized rats given an excess of salt in their drinking water but not in those given plain water (151). Hypertensive responses to catecholamines and other pressor agents were increased in rats made hypertensive with desoxycorticosterone and excess salt (222). A decreased pressor response to norepinephrine has been observed in normotensive subjects following the saluresis produced by chlorothiazide (154, 238). That the latter may be due to the diminished plasma volume produced by this agent is suggested by the fact that normal reactivity is restored after replenishing the plasma volume with isoosmotic, salt-free dextran solution (238).

Using the ballistocardiogram as a rough index of cardiac output Wolf *et al.* (253) found two patterns of response to stressful interview. An 'exercise' pattern, in which the rise of blood pressure was accompanied by ballistocardiographic and pulse pressure changes suggesting an increase in stroke volume, was associated with overt emotional responses and was seen in both hypertensive and normotensive patients. A 'high resistance' pattern occurred when the patient exhibited a

calm exterior but was repressing emotional turmoil, and was seen frequently in hypertensive patients. It is suggested that the latter might lead to essential hypertension. Using the dye method for measuring cardiac output in normotensive subjects Brod *et al.* (25) also found either no change or an increase in cardiac output in the pressor response to stresses such as the cold pressor test and problems in mental arithmetic. Renal blood flow decreased while muscle blood flow increased. They postulate a ubiquitous response to stresses of all types characterized by visceral vasoconstriction and voluntary muscle vasodilation. The directional change in total peripheral resistance depends on which predominates, and also on the cardiac output.

The Russian literature recently reviewed by Simonson and Brožek contains numerous references to vascular reactivity in hypertension (210). Exaggerated vasoconstriction in the hand or forearm in response to cold, or to the verbal signal for the application of cold in a conditioned response, and to mental arithmetic, has been noted. Such heightened reactivity could be explained by abnormally increased vasomotor discharges of cerebral origin (the Russian view), by augmented vascular responsiveness to normal rates of vasomotor discharge, by reduced buffering activity of the moderator reflexes, or by purely mechanical factors. In regard to the latter, decreased vascular distensibility would produce a steeper rise in pressure for a given increase in cardiac output. Also, resistance increases approximately as the inverse of the fourth power of the radius. In the narrower vessels of the hypertensive patient resistance change would be greater for a given decrease in radius (183). The question as to whether one or all of these mechanisms produces the heightened lability of blood pressure and increased vascular reactivity in some hypertensive patients remains to be determined.

EXAGGERATED NATRIURESIS

In 1946 Farnsworth (62) noted excessive chloride excretion during salt loading in hypertensive as compared with normotensive patients. Green *et al.* (92) and subsequently others (19, 46, 114, 9) found an exaggerated natriuresis following saline infusions. The natriuresis was accompanied by a diuresis. A similar response has been observed in normotensive patients with mitral stenosis (28).

Hypertensive patients seem to be unusually responsive to even moderate expansion of their plasma and extracellular fluid volumes. Baldwin *et al.* (9) observed that increased sodium excretion can be induced without sodium, osmotic or water loading by infusion of inulin and *p*-aminohippurate at a rate of 2 milliliters per minute (total volume of 90 ml). Other investigators corroborate Baldwin's observation that the exaggerated natriuresis is not dependent on sodium loading alone, as it has been observed following infusion of mannitol (26) or 5 per cent glucose in distilled water, or after the oral ingestion of water or beer (57).

Baldwin (9) further observed that the normotensive subject could be made to respond with a natriuresis if the hypertonic saline infusion was prolonged to 2 hours. It has been observed in normal individuals that a massive oral water load can induce a delayed natriuresis (133, 134). Cortisone pretreatment, which also produces an expansion of extracellular and plasma volumes, will cause the normo-

tensive subject to respond to a hypertonic saline load with exaggerated natriuresis (19). These observations suggest that the normotensive subject requires greater filling of his plasma and/or total extracellular fluid space to elicit the natriuretic response. There is no evidence, however, for an increased extracellular fluid space in uncomplicated hypertension (237, 128, 51, 187).

The natriuretic response to a salt load does not seem to be related to changes in glomerular filtration rate or renal plasma flow (9, 43) or to a renal tubular defect (9). Hypertensive patients were not salt losers under normal basal conditions. Under salt deprivation the urinary excretion of sodium falls to low levels in hypertensive subjects. Finally, Baldwin (9) showed that exaggerated natriuresis following salt load can be abolished in hypertensive patients by pretreatment with a low sodium diet, a maneuver which, incidentally, reduces plasma and extracellular fluid volumes (159, 163, 239).

Hollander and Judson (115) found that the natriuresis of hypertensive subjects is significantly reduced toward normal by antihypertensive drug therapy. This reduction appeared to result from an alteration in renal tubular activity, since the calculated load of filtered sodium was not significantly different after than before treatment. Thompson *et al.* observed that reduction of blood pressure after sympathectomy also decreased sodium excretory capacity (225). Selkurt (204) and Epstein (59) believe that the rate of sodium excretion is governed by the arterial pressure, a view to which Hollander and Judson concur.

The importance of the arterial pressure and other questions relating to the fundamental mechanisms controlling natriuresis in man have been reviewed by Smith (214). He concludes that the factors controlling sodium conservation are unknown, but that among them is either the volume of extracellular fluid or the degree of filling of the arterial tree. Exaggerated natriuresis secondary to glucose and water loading has been observed also in normotensive patients with mitral stenosis without heart failure (28). This suggests that exaggerated natriuresis may not depend on an elevated arterial pressure but on some other hemodynamic abnormality lying retrograde to the mitral valve. Stretch receptors in the left atrium have been implicated in stimulating diuresis but not natriuresis (110).

More recently Bartter (12) has indicated that aldosterone secretion in the dog depends in part upon a function of intravascular volume. Aldosterone secretion increased when the central blood volume was reduced and decreased when the central volume was expanded. Mills *et al.* (155) believe that the decrease in aldosterone secretion produced by central blood volume expansion is mediated through the vagus, whereas according to Bartter (13) the pathway which stimulates aldosterone secretion begins in baroreceptor nerve endings in the thyroid-carotid bifurcation. These results have appeared only in preliminary form and need further documentation. It also should be pointed out that the adrenal response is rather slow, since significant changes in aldosterone secretion were not detected until approximately 30 minutes following the change in central blood volume. On the other hand, sodium conservation by the kidney begins almost immediately after a reduction of blood volume or blood pressure.

It also has been proposed recently that sodium reabsorption in the kidney

may be related directly to the percentage of renal plasma flow filtered at the glomeruli (233). With this in mind Baldwin's data (9) were reexamined to determine whether the filtration fraction in hypertensive patients behaved abnormally during intravenous salt loading. However, as calculated from his results, the changes in filtration fraction during the natriuretic responses were essentially similar in hypertensive and normotensive subjects.

In summary, exaggerated natriuresis occurs in the hypertensive subject with only slight excess hydration which need not contain salt. In the normal subject a similar natriuresis occurs only under more prolonged and a considerably greater degree of hydration, requiring excess saline infusion, massive oral water hydration or cortisone pretreatment. All of these factors produce some expansion of plasma and extracellular fluid volumes, but the degree of expansion required in the hypertensive seems to be far less than in the normotensive individual. These observations suggest that the relationship between the vascular capacity and the blood volume might be disturbed in hypertension. The findings of Hollander and Judson that antihypertensive agents eliminate the natriuretic response does not rule out the concept of disproportion between blood volume and vascular capacity in hypertensive patients, since some antihypertensive agents, particularly the ganglion blocking drugs, increase peripheral vascular capacity (197, 186, 232).

SUMMARY

The work of the heart increases greatly in hypertension, due primarily to the elevation of systolic pressure. The principal mechanism of cardiac adaptation to this increased load is myocardial hypertrophy, by means of which intrinsic myocardial tension is augmented. In the open chest dog subjected to a sudden rise of peripheral resistance, compensation is restored by an increase in the residual volume of the left ventricle. However, direct evidence is lacking that this represents the method of adaptation in chronic hypertension. Clinically evident cardiac dilatation frequently is not seen until some evidences of decompensation appear. Dilatation of the heart may further increase the tension requirements of the left ventricular myocardium through the operation of the law of Laplace.

There is no evidence at present that myocardial 'contractility' is augmented by increased sympathetic discharge to the heart, as has been demonstrated during exercise in the intact animal. However, the possibility that some cases of hypertension may be initiated by an increase in cardiac output or intraventricular pressure operating through such a mechanism has not been ruled out. The cardiac reserve in hypertensive patients bears no relation to the height of the blood pressure and remains normal until cardiac dilatation and symptoms of failure supervene.

The increase in pulse pressure in the presence of a normal cardiac output indicates loss of large artery distensibility. This appears to be brought about in chronic hypertension by passive distention, accelerated atherosclerosis and, occasionally, by degenerative changes in elastic tissue. As a result of these changes pulsatile pressures are transmitted farther than normally into the peripheral circulation.

The principle physical factors governing the peripheral resistance are those represented in the Poiseuille equation plus the distensibility of blood vessel walls. The change in apparent viscosity of the blood in small vessels appears to be an unimportant factor. As vessels constrict and their radii become smaller less tension energy is required in their walls to counteract the blood pressure. The peripheral resistance includes not only the arterioles but also the capacity vessels, precapillary sphincters and arteriovenous anastomoses, although the major site of resistance is in the arterioles.

From measurements of cardiac output and mean arterial pressure the calculated total peripheral resistance is increased in about two-thirds of the cases of chronic human hypertension. It is not certain whether the remainder represent a group in which an elevation of cardiac output is the primary hemodynamic fault or whether apprehension associated with the procedure disturbed the basal hemodynamic state. The elevated peripheral resistance in hypertension is more or less uniformly distributed throughout the body and does not appear to be the result of augmented activity of vasomotor nerves. The peripheral vessels have a considerable degree of autonomy in regulating local resistance. In coarctation of the aorta peripheral resistance is adjusted differently in the upper and lower halves of the body to provide normal blood flows to each region, but the factors controlling this adjustment ('myogenic' response, tissue metabolites, local oxygen tensions) are not known. Recent work suggests that the baroreceptor reflexes are reset at a higher level in chronic hypertension. This resetting combats deviations from the existing hypertensive level but does not imply that the hypertension is initiated by or is dependent upon increased vasoconstrictor nerve activity.

Direct observations of the small vessels in limited areas such as the conjunctiva and nailfold indicate that the capillaries often are narrowed and sparse in distribution. Convincing evidence is lacking that the increased peripheral resistance is produced by 'waterlogged' arterioles; the role of sodium in chronic hypertension is still obscure and may involve nothing more than the reduction of plasma and extracellular fluid volumes which occurs during sodium depletion.

Sympathetic stimulation and catecholamines constrict postarteriolar as well as arteriolar vessels. There is only suggestive evidence that the capacity vessels also may be contracted in chronic hypertension.

Many but not all hypertensive patients exhibit increased vascular reactivity to stressful stimuli and to a lesser extent to vasopressor agents. However, the moving forces involved are far from clear. The equally puzzling phenomenon of exaggerated natriuresis in hypertension may be associated with the elevated arterial pressure, per se, or with some function of the vascular volume.

Hypertension is truly 'a riddle wrapped in a mystery inside an enigma.' By outlining the areas of ignorance in this one aspect (hemodynamics) some footholds may be found to aid in further exploration.

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